

# Peripheral artery disease patients may benefit more from aggressive secondary prevention than aneurysm patients to improve survival



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## ABSTRACT

**Background and aims:** Although it has become clear that aneurysmal and occlusive arterial disease represent two distinct etiologic entities, it is still unknown whether the two vascular pathologies are prognostically different. We aim to assess the long-term vital prognosis of patients with abdominal aortic aneurysmal disease (AAA) or peripheral artery disease (PAD), focusing on possible differences in survival, prognostic risk profiles and causes of death.

**Methods:** Patients undergoing elective surgery for isolated AAA or PAD between 2003 and 2011 were retrospectively included. Differences in postoperative survival were determined using Kaplan-Meier and Cox regression analysis. Prognostic risk profiles were also established with Cox regression analysis.

**Results:** 429 and 338 patients were included in the AAA and PAD groups, respectively. AAA patients were older (71.7 vs. 63.3 years,  $p < 0.001$ ), yet overall survival following surgery did not differ (HR: 1.16, 95% CI: 0.87–1.54). Neither was type of vascular disease associated with postoperative cardiovascular nor cancer-related death. However, in comparison with age- and gender-matched general populations, cardiovascular mortality was higher in PAD than AAA patients (48.3% vs. 17.3%). Survival of AAA and PAD patients was negatively affected by age, history of cancer and renal insufficiency. Additional determinants in the PAD group were diabetes and ischemic heart disease.

**Conclusions:** Long-term survival after surgery for PAD and AAA is similar. However, overall life expectancy is significantly worse among PAD patients. The contribution of cardiovascular disease towards mortality in PAD patients warrants more aggressive secondary prevention to reduce cardiovascular mortality and improve longevity.

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## 1. Introduction

Traditionally, dilatation and occlusion were considered to represent two extremes on the same spectrum of arterial disease. As such, it was presumed that both entities were the result of extensive atherosclerosis [1]. This assumption was largely based on the fact that the two vascular diseases share a number of risk factors, such as smoking, hypertension, and older age [2–6].

However, over the years, disparities in etiologic cardiovascular risk profiles were demonstrated [7–11], as well as differences in the

severity of atherosclerotic burden between patients suffering from aneurysmal and occlusive disease [7,12–16]. In addition, differences in cytokine levels, inflammation, and enzyme activity were found in the arterial walls affected by aneurysmal or occlusive disease [9,17,18]. Also, recent studies show that genetic susceptibility, rather than environmental risk factors, plays a particularly important role in the pathogenesis of aneurysmal disease [19–21]. Although it is becoming clear that aneurysm formation and atherosclerosis are two separate clinical entities, it remains unclear whether this also translates into long-term prognostic differences between the two patient categories. Differences in long-term outcome, particularly of cardiovascular nature, would warrant more aggressive secondary prevention regimens for those at the highest risk.

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With surgical treatment as a uniform indicator of severe disease, we aim to determine the long-term vital prognosis for abdominal aneurysmal and peripheral occlusive disease patients, focusing on possible differences in survival, risk profiles, and causes of death.

## 2. Patients and methods

Patients undergoing elective surgery for AAA or PAD at the Erasmus University Medical Centre in Rotterdam between January 2003 and December 2011 were retrospectively identified using operation codes and surgical reports. Long-term survival was assessed from the day of surgery onward. In order to improve homogeneity in terms of operative stress and severity of disease, all percutaneous endovascular procedures, i.e. percutaneous endovascular aneurysm repair (EVAR) and percutaneous lower limb PTA or stenting procedures, were excluded. AAA patients who underwent prior endovascular or open surgical revascularization for lower limb ischemia were excluded from this study. PAD patients who underwent prior treatment of an abdominal or thoracic aortic aneurysm were also excluded. Treatment indications for AAA and PAD were both in accordance with the European Society for Vascular Surgery guidelines [22,23]. Similarly, all vascular surgery patients were treated in accordance with these guidelines regarding secondary cardiovascular prevention. As a result, all patients followed a lifelong regimen of anti-platelets and statins, as well as anti-hypertensive and anti-diabetes medication on indication. Baseline characteristics were obtained from hospital charts and included age, gender, comorbidity, prior vascular interventions, smoking status (current/former or non-smoker), and body mass index (BMI). Institutional approval for this study was obtained, and no informed consent was required according to local directives for retrospective studies. The study complies with the Helsinki declaration on research ethics.

### 2.1. Definitions

Diabetes mellitus was recorded if diabetes was mentioned in the medical history or if patients used insulin or oral anti-diabetics. Hypertension was defined as blood pressure >140/90 mmHg or use of anti-hypertensive medication. A history of cancer was defined as past or current malignant neoplastic disease, except for basal cell carcinoma. Renal insufficiency was defined as an estimated glomerular filtration rate (eGFR) < 60 ml/min as calculated from preoperative serum creatinine levels using the MDRD formula. Smoking status and BMI were derived from the medical records. Cerebrovascular disease was defined as mentioning of symptomatic carotid artery disease (i.e., transient ischemic attack or stroke) and/or a carotid endarterectomy or stenting procedure in the medical history. Ischemic heart disease was considered if one of the following was present: reference to previous cardiac ischemic events in cardiology notes, prior coronary intervention or evidence of myocardial ischemia in provocative pre-operative tests (dobutamine stress echocardiography or myocardial scintigraphy). Prior vascular interventions were defined as either surgical or percutaneous vascular treatment prior to the index operation, not including coronary revascularization.

### 2.2. Endpoints

The primary endpoint was overall mortality. Secondary endpoints were cardiovascular and cancer-related death.

### 2.3. Cause of death

Causes of death were obtained from the Dutch Central Bureau of

Statistics (CBS). A database consisting of medical data on the study participants was anonymized by authorized data managers employed by CBS. This data set was subsequently imported and linked to the Dutch death registry, which is maintained by the CBS. According to Dutch privacy legislation, data analysis was only allowed to authorized researchers (KU, FBG) from designated institutions inside a secure environment after approval from the institutional ethical committee. Furthermore, output was checked by the CBS for privacy violations before it was allowed for publication purposes. Autopsy was not routinely performed. The cause of death was defined as the initial cause of health deterioration, consequently resulting in death. This approach is similar to the strategy used for the overall Dutch population. The causes of death were grouped according to the *International Classification of Diseases, 10th Revision* (ICD-10). For cardiovascular death, the following codes were used: I10–I79; for cancer-related death: C00–C43, C45–C97, D00–D03, and D05–09; for death due to obstructive pulmonary disease: J40–J47; and for digestive system-related causes: K00–K93.

For survival estimation in the general population, a comparative age and gender matched control group was derived from civil registries of the Dutch population –also maintained by the CBS– for both the AAA and PAD group separately. To assess differences in causes of death compared to the general population, deaths in the respective study groups were individually matched on demographic properties to cause of death distributions in the general population. For example, if deaths in the AAA group consisted for 5% of males between the aged between 80 and 85 at the time of death, the AAA matched cohort corresponds proportionally to the death distribution for males with the same age and gender characteristics from the general population.

### 2.4. Statistical methods

Baseline characteristics were described as counts and percentages (dichotomous variables), or means and standard deviations (continuous variables). Differences at baseline were determined using Pearson's chi-square analysis and student t-test, where appropriate. Survival for the aneurysmal and occlusive disease cohorts was initially assessed using Kaplan-Meier and log-rank analyses. Differences in the vital prognosis were subsequently investigated using adjusted Cox proportional hazards regression. Multivariable analyses adjusted for demographics, comorbidities, and other risk factors (age, gender, diabetes mellitus, ischemic heart disease [IHD], history of cancer, renal insufficiency, BMI, and current smoking). The AAA group was designated as the reference category in these analyses. Prognostic risk profiles for the two study groups were established by determining hazard ratios for potential risk factors separately for the AAA and PAD group using Cox proportional hazards model. Univariately significant covariates were included in the multivariable model. All tests were two-sided and significance was considered when  $p$ -value < 0.05. Statistical analysis was performed using the SPSS Statistics 20 (IBM Inc., Chicago, IL).

## 3. Results

A total of 470 patients undergoing elective surgery for AAA and 353 patients for PAD were identified. In the AAA group, 40 patients were excluded because of prior treatment for PAD, while 14 patients were excluded in the PAD group for prior aneurysm treatment. Two patients, one in each treatment group, were excluded due to unavailable follow-up data as a result of emigration. The remaining 429 AAA and 338 PAD patients were considered suited for analysis.

### 3.1. Baseline characteristics

Baseline characteristics are detailed in Table 1. Compared to the PAD group, AAA patients were older at the time of surgery (71.7 vs. 63.3 years,  $p < 0.001$ ), and more often male (88% vs. 66%,  $p < 0.001$ ). In addition, patients in the AAA group were more commonly affected by cancer (21% vs. 14%,  $p = 0.025$ ) and renal insufficiency (29% vs. 20%,  $p = 0.006$ ). Conversely, diabetes and current smoking were less common among AAA patients (16% vs. 30%,  $p < 0.001$  and 38% vs. 49%,  $p = 0.003$ , respectively). AAA patients also less frequently underwent vascular interventions prior to the index operation (4% vs. 46%,  $p < 0.001$ ).

### 3.2. Overall survival

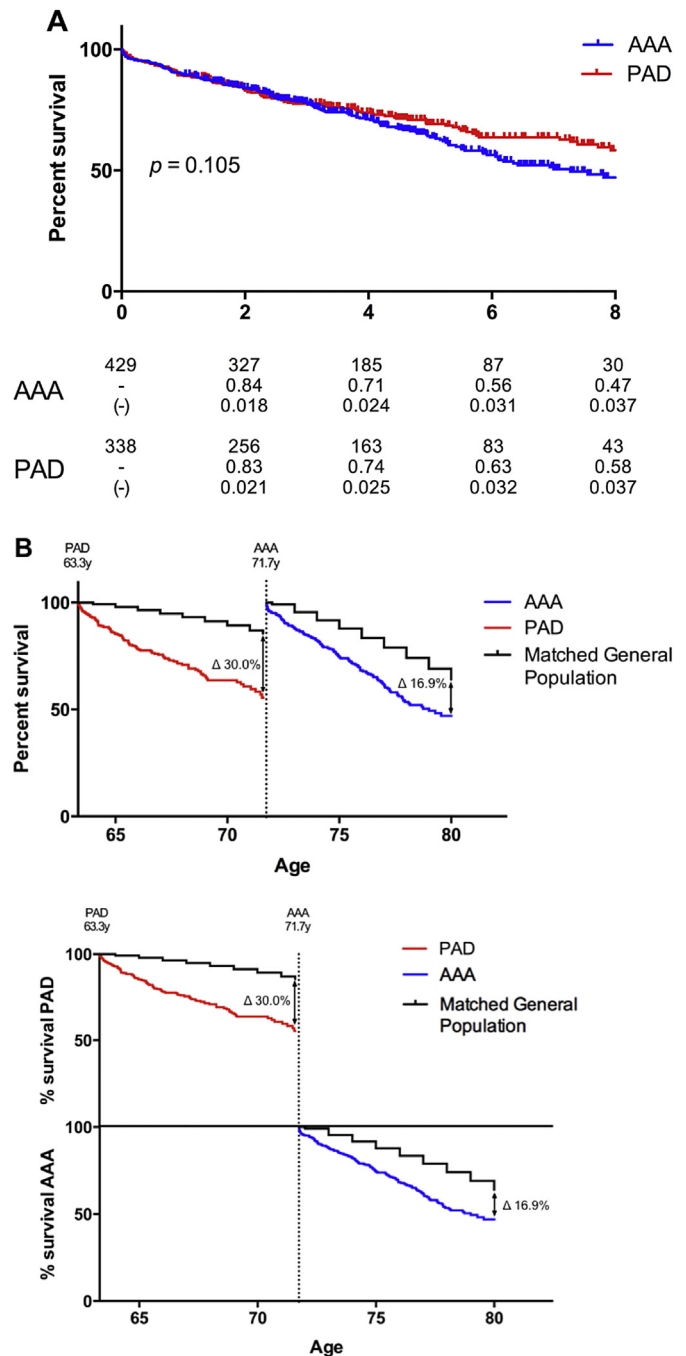
During a median follow-up of 3.6 years after surgery (IQR: 2.1–5.4 years) 154 patients died in the AAA group. For PAD patients, median follow-up time was 3.8 years (IQR: 2.0–5.9 years), during which 107 patients died. Postoperative survival proved to be similar for the two groups, in both unadjusted analysis, as determined by log-rank testing ( $p = 0.105$ ; Fig. 1A), as well as adjusted Cox-regression analysis (HR: 1.16, 95% CI: 0.87–1.54, Table 2). However, since AAA patients were substantially older at the time of intervention (71.7 vs. 63.3 years), postoperative survival did not adequately reflect life expectancy of the respective groups. Fig. 1B represents the postoperative life expectancies for the two groups with the average age at the time of treatment as the starting point. A direct comparison with a Dutch general population with similar age and gender properties shows that in particular survival in the PAD cohort more strongly deviates from its matched general population (30.0% vs. 16.9%, respectively), indicating more life years lost as compared to the AAA cohort.

### 3.3. Cause of death

Causes of death could be obtained for 153 out of 154 patients (99.4%) in the AAA group and for all 107 deceased patients in the PAD group. Deaths were classified in five categories: cardiovascular, cancer-related, chronic obstructive pulmonary disease (COPD), intestinal disease, and other causes (Fig. 2). Cardiovascular mortality was the leading cause of death in both AAA and PAD patients (35.3% vs. 39.3%,  $p = 0.944$ ), followed by cancer-related death (28.8% vs. 24.3%, respectively,  $p = 0.220$ ). However, cardiovascular mortality encompasses a much larger proportion in the PAD group as compared to the age- and gender-matched general population

**Table 1**  
Baseline characteristics per study group.

Variable	AAA (n = 429)	PAD (n = 338)	p-value
<b>Demographics</b>			
Female gender – n (%)	51 (12)	114 (34)	<0.001
Age – (years, mean $\pm$ SD)	71.7 $\pm$ 7.5	63.3 $\pm$ 11.1	<0.001
<b>Cardiovascular risk factors</b>			
Diabetes – n (%)	67 (16)	102 (30)	<0.001
Hypertension – n (%)	291 (68)	231 (69)	0.782
Current smoking – n (%)	161 (38)	164 (49)	0.003
Body mass index – (mean $\pm$ SD)	26.2 $\pm$ 4.1	25.8 $\pm$ 4.6	0.217
Peripheral artery disease – n (%)	40 (9.3%)	338 (100%)	–
<b>Comorbidities</b>			
History of cancer – n (%)	88 (21)	48 (14)	0.025
Ischemic heart disease – n (%)	203 (47)	152 (45)	0.512
Coronary revascularization – n (%)	92 (21)	80 (24)	0.613
Cerebrovascular disease – n (%)	73 (17)	52 (15)	0.544
Renal insufficiency – n (%)	125 (29)	69 (20)	0.006
History of vascular interventions – n (%)	19 (4)	157 (46)	<0.001



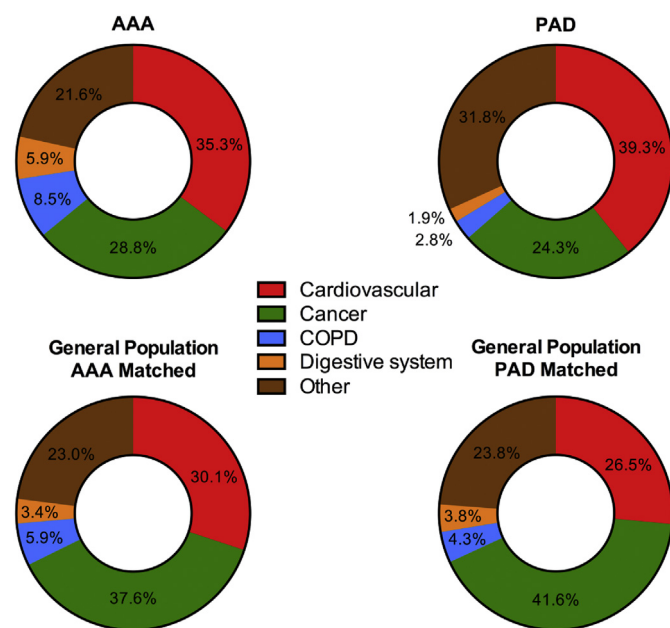
**Fig. 1. Long-term survival analysis for postoperative survival after AAA and PAD.** (A) Kaplan-Meier analysis comparing survival after surgical intervention for AAA and PAD. (B) Postoperative life expectancy for patients treated for AAA and PAD. The starting points of the survival curves correspond to the average age at intervention in the study groups (i.e. 63.3 and 71.7 years, respectively in the PAD and AAA groups). Survival estimates of the general population are age- and gender-adjusted in accordance with the respective cohorts.

(39.3% vs. 26.5%) than in the AAA group (35.3% vs. 30.1%). Death due to intestinal disease or other causes was similar in the AAA and the PAD group (5.9% vs. 1.9%,  $p = 0.124$ ; 21.6% vs. 31.8%,  $p = 0.249$ , respectively). Mortality resulting from COPD, however, was significantly more common among AAA patients compared to PAD patients (8.5 vs. 2.8%,  $p = 0.043$ ).

Risk adjusted survival analysis was additionally performed to assess whether cause-specific mortality risks differed between AAA

**Table 2**  
Adjusted survival analysis for overall and cause-specific mortality. The AAA group served as the reference category.

	Univariate		Multivariate	
	HR	95% CI	HR	95% CI
Overall death	0.82	0.64–1.04	1.16	0.87–1.54
Cardiovascular death	0.91	0.61–1.37	1.47	0.93–2.31
Cancer-related death	0.70	0.43–1.14	1.14	0.64–2.03



**Fig. 2.** Cause of death distribution in the AAA and PAD groups and an age- and gender-matched general Dutch population.

and PAD patients. These analyses showed that no difference exists in risks of cardiovascular and cancer-related death between treatment groups (HR: 1.47, 95% CI: 0.93–2.31; HR: 1.14, 95% CI: 0.64–2.03, respectively, Table 2). For causes of death with smaller proportions, adjusted survival analysis was not possible due to limited number of events.

### 3.4. Risk profile all-cause mortality

Risk profile analysis was performed for the two study groups separately (Table 3). In the AAA group, univariately significant risk factors that proved to be independently associated with increased

mortality were age (HR: 1.70, 95% CI: 1.34–2.15, per 10 year increase), history of cancer (HR: 2.44, 95% CI: 1.72–3.46) and renal insufficiency (HR: 1.78, 95% CI: 1.27–2.51). Higher BMI was protective against mortality (HR: 0.93, 95% CI: 0.89–0.97, per BMI unit increase). Ischemic heart disease appeared to negatively affect survival of AAA patients in univariable analysis, but this effect was lost in the multivariable model (HR: 1.33, 95% CI: 0.95–1.85).

Similar risk factors found in the PAD cohort were age (HR: 1.30, 95% CI: 1.08–1.57, per 10 year increase), a history of cancer (2.26, 95% CI: 1.45–3.54) and renal insufficiency (HR: 1.57, 95% CI: 1.02–2.42). Additionally, diabetes (HR: 1.69, 95% CI: 1.14–2.50) and ischemic heart disease (HR: 1.76, 95% CI: 1.18–2.60) worsened survival of PAD patients. Hypertension was a significant predictor of mortality in univariable analysis in the PAD group, but could not be established as an independent risk factor in the adjusted model (HR: 1.18, 95% CI: 0.75–1.85).

## 4. Discussion

This study demonstrates that postoperative survival is similar for patients undergoing surgery for aneurysmal or atherosclerotic occlusive arterial disease, despite the fact that PAD patients were almost 10 years younger at the time of surgery. The mortality rate of PAD patients was much higher than that of AAA patients as compared to their respective age- and gender-matched general populations. These data indicate a relatively greater loss of life years in PAD patients as compared to AAA patients.

What causes this difference in life expectancy between PAD and AAA patients? The leading causes of death, i.e. cardiovascular disease and cancer, were similar in the two patient groups in unadjusted as well as adjusted analyses. This is in agreement with a study from the REACH registry, showing no difference in 1-year cardiovascular death between the two patient groups [8]. Interestingly, however, the proportion of cardiovascular mortality in PAD patients was almost 50% higher than in the age- and gender-matched general population, whereas in the AAA group the difference with the general population was rather small. This suggests that cardiovascular disease is a relatively more important determinant of life expectancy in PAD when compared to AAA patients in spite of their younger age. These findings are in line with previous studies showing more severe systemic atherosclerosis – reflected by increased carotid intima-media thickness – in patients with occlusive arterial disease as compared to those with AAA [7,12–16]. Interestingly, it has been demonstrated that as little as a tenth of a millimeter increase in arterial wall thickness is already associated with considerable increases in risk of myocardial infarction, stroke, and even death [24–27]. In PAD patients, a relatively severe progression of atherosclerotic disease is therefore likely to be responsible for the similar survival compared to the much older

**Table 3**  
Risk profiles for all-cause mortality for the AAA and PAD group.

Variables	AAA				PAD			
	Univariate		Multivariate		Univariate		Multivariate	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Age per 10 year incr.	1.83	1.47–2.30	1.70	1.34–2.15	1.47	1.22–1.76	1.30	1.08–1.57
Gender	1.06	0.64–1.76	–	–	1.15	0.77–1.70	–	–
Diabetes	0.91	0.58–1.45	–	–	2.03	1.38–2.99	1.69	1.14–2.50
IHD	1.41	1.03–1.94	1.33	0.95–1.85	2.01	1.36–2.96	1.76	1.18–2.60
Cancer	2.57	1.84–3.59	2.44	1.72–3.46	3.14	2.04–4.82	2.26	1.45–3.54
Renal insufficiency	1.96	1.42–2.71	1.78	1.27–2.51	2.46	1.64–3.69	1.57	1.02–2.42
Hypertension	1.39	0.98–1.97	–	–	1.62	1.04–2.52	1.18	0.75–1.85
BMI per unit incr.	0.93	0.89–0.97	0.93	0.89–0.97	1.03	0.98–1.07	–	–
Current smoking	0.90	0.65–1.25	–	–	0.93	0.64–1.37	–	–



AAA patients, and the poor prognosis compared to the matched general population. Of note, COPD-related death was more frequent among AAA patients, which may be due to a common -genetically determined- defect in the extracellular matrix [28,29]. This further supports the divergence in pathophysiology between aneurysmal and occlusive vascular disease.

In order to identify what drives mortality in the respective groups, we compared their mortality risk profiles. These analyses showed that age was more than twice as important for AAA patients as compared to PAD patients (HR: 1.70 vs. 1.30, per 10 year increase). Conversely, a history of ischemic heart disease and the presence of diabetes were more important for the prediction of death in PAD patients. Besides hazardous risk estimators, we found that higher BMI was associated with prolonged survival in the AAA group. This phenomenon, known as the obesity paradox, has been described multiple times in many different study populations. Although the exact mechanism for this phenomenon remains unknown, the association between chronic disease and malnutrition is believed to play a role [30,31]. The hazard ratios of 0.9 for current smoking and diabetes in univariate analysis appear to represent a protective effect of these factors for mortality. However, the wide confidence intervals indicate that rather no association existed between these factors and mortality.

Since cardiovascular risk factors, as opposed to age, are potentially modifiable, this provides the opportunity to improve life expectancy in PAD patients. Regrettably, in spite of widespread guidelines for cardiovascular risk management and the undeniable benefits of secondary prevention, studies such as the REACH registry show that PAD patients do not achieve adequate risk factor control as frequently as individuals with coronary or cerebrovascular disease [32], despite comparable risks of future cardiovascular events. Pande et al. found that only 27% of primary PAD patients were on antiplatelet therapy, and a mere 19% received statins [33]. Thus, there is still a large gap between therapeutic goals and current secondary preventive care for PAD patients [34,35]. Furthermore, tight control of blood pressure (i.e.  $\leq 130$ – $135$  mmHg), as opposed to relaxed control (i.e.  $\leq 140$  mmHg), is associated with a further reduction in cardiovascular morbidity and mortality [36,37]. The recent SPRINT trial even determined that blood pressure control with a target of  $<120$  mmHg resulted in a 43% reduction in cardiovascular mortality [38]. Similarly, tight regulation of blood glucose and lipids has been reported to improve the overall and cardiovascular prognosis [39–41]. In light of these benefits, narrowing of the tolerable margins of these classical cardiovascular risk factors should be considered, particularly in PAD patients.

This study has limitations that should be addressed. First, this study is of retrospective nature, which has inherent limitations with regard to data collection. Also, it should be considered that only patients who underwent surgery were identified. Patients treated conservatively, or by less invasive -percutaneous- techniques, and those with prohibitive surgical risks were not included in this study. Although this approach provided more uniformity in terms of severity of disease and operative risks, a selection bias towards patients suited for surgery may have resulted. Also, Dutch law prohibits the documentation of ethnicity in medical records, which precluded its consideration in this study. For reference, a review of the ethnical proportions in the Dutch general population showed that 77.8% is of Dutch descent, 6.2% African descent, and 7.0% Mediterranean descent. In addition, it is virtually impossible to determine the onset of aneurysmal or atherosclerotic disease. As surgical treatment is a uniform indicator of severe disease, long-term survival was assessed from the day of surgery onward. PAD patients more often underwent some kind of revascularization prior to the index operation in this study, which indicates that the age difference demonstrated for timing of the index operation

between occlusive and aneurysmal disease may even underestimate the difference in the age at onset between the two respective diseases. This adds support to the argument that AAA and PAD are two distinct entities. Finally, the increasing utilization of endovascular treatment approaches warrants evaluation and comparative assessment of the postoperative prognosis following minimally invasive AAA and PAD treatment under local anesthesia.

In conclusion, this study shows that aneurysmal and occlusive vascular disease do not only differ in terms of etiology and pathophysiology, but are also distinct entities in terms of prognosis. Life expectancy in PAD patients is shorter and is predominantly reduced by cardiovascular morbidity, as opposed to age in AAA patients. This warrants emphasis on aggressive cardiovascular risk factor modification particularly for PAD patients in order to maximize longevity.

### Conflict of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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